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PRE-APPEAL BRIEF REQUEST FOR REVIEW

Docket Number (Optional)
054822-0117

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to "Mail Stop AF, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450" [37 CFR 1.8(a)]

On April 27, 2010

Signature

Typed or printed name

Application Number	Filed
10/805,788	3/22/2004

First Named Inventor
Steven C. Quay

Art Unit	Examiner
1654	Thomas Sweeney Heard

Applicant requests review of the final rejection in the above-identified application. No amendments are being filed with this request.

This request is being filed with a notice of appeal.

The review is requested for the reason(s) stated on the attached sheet(s).
Note: No more than five (5) pages may be provided.

I am the

☐ applicant/inventor.

Jacqueline D. Wright Bonilla
Signature

☐ assignee of record of the entire interest.
See 37 CFR 3.71. Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

Jacqueline D. Wright Bonilla
Typed or Printed Name

☒ attorney or agent of record.
Registration number 45,239

(202) 295-4792
Telephone Number

☐ attorney or agent acting under 37 CFR 1.34.
Registration number if acting under 37 CFR 1.34

April 27, 2010
Date

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below*.

☒ *Total of 1 forms are submitted.

Atty. Dkt. No. 054822-0117

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Steven C. Quay et al.

Title: NASAL CALCITONIN FORMULATIONS CONTAINING CHLOROBUTANOL

Appl. No.: 10/805,788

Filing Date: 3/22/2004

Examiner: Thomas Sweeney Heard

Art Unit: 1654

Confirmation Number: 9945

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the New **Pre-Appeal Brief Conference Pilot Program**, announced July 11, 2005, this Pre-Appeal Brief Request is being filed together with a Notice of Appeal.

REMARKS

The Examiner has rejected claims 8, 12, 16 and 20-30 as allegedly being obvious over EP 0115627 ("APC"), U.S. Pat. No. 5,759,565 ("Azria") and U.S. Pat. No. 5,026,825 ("Grebow"). Applicants maintain that Azria teaches away from the claimed invention, and that the Examiner has relied upon impermissible hindsight reasoning to support his rejection.

All independent claims at issue (claims 8, 12, 16, 29 and 30) recite a calcitonin composition suitable for intranasal administration "consisting of" certain recited elements.

Independent claims recite amounts of calcitonin (as an aqueous solution, or also recite water), chlorobutanol and sodium chloride, as well as certain other elements, i.e., having a pH of about 4 or less, and in some claims less than about 5% oxygen, or optionally hydrochloric acid. Every independent claim requires chlorobutanol at a concentration of between about 0.25% and about 0.4% weight/weight.

The references cited by the Examiner disclosed the use of chlorobutanol as a preservative. *See* APC, page 3, lines 40-55; Azria, col. 2, lines 35-51; Grebow, col. 12, lines 1-16. During prosecution, however, the Examiner acknowledged that "Azria teaches that concentration[s] of chlorobutanol above 0.6% have undesired effects." Final Office Action at 4. Specifically, Azria taught that 0.6% chlorbutanol caused "more than 50% inhibition of the ciliary beating frequency of rat trachea within 20 minutes ...," and that "these are just some of the disadvantageous effects that can be encountered." Azria, col. 2, lines 46-51.

In addition, after noting that not all preserving agents are suitable, Azria also stated generally that "chlorbutanol was found to attack rubber stoppers and other joints used in nasal spray applicators between the spray pump and a bottle." Azria, col. 2, lines 42-45. Moreover, Azria expressly taught that chlorbutanol at 0.6% in calcitonin nasal pharmaceutical compositions showed insufficient activity against the test fungus *Pen. steckii*, more than 3 days being required to reduce the cell count to less than 0.1%. *Id.* at col. 2, lines 37-42.

That not withstanding, the Examiner asserted that it would have been obvious to use chlorobutanol as a preservative at "%w/v concentrations below that of 0.6% to prevent any deleterious effects in the composition." Office Action at 5. The Examiner also contended that APC teaches the use of chlorobutanol in the range of 0.001-2.0% w/v and that Grebow teaches the use of chlorobutanol in ranges from "0.5-1.0 and in Example 9, teaches Chlorobutanol at 0.1% w/v." Office Action at 4 and 5. The Examiner then concluded that APC and Grebow "teach a specific example where chlorobutanol is used at much lower concentrations as a preservative...." Office Action at 8. The Examiner further alleged that "it is clear from Azria et al that chlorobutanol has a deleterious effect at 0.6% and higher, but there is no indication that

this would be true for concentrations lower that [*sic*] the 0.6% that Azria et al teaches...." Office Action at 8.

As explained above, Azria expressly disclosed that at concentrations of 0.6%, chlorobutanol was ineffective as a preservative. Specifically, "chlorobutanol at 0.6% in calcitonin nasal pharmaceutical compositions showed insufficient activity against the test fungus *Pen. steckii*...." Azria, col. 2, lines 39-41. Moreover, those skilled in the art reading Azria would have concluded that chlorobutanol did not work as a preservative at concentrations lower than 0.6% because it failed to work as a preservative at concentrations as high as 0.6%. This fact is supported by the Declaration of Henry R. Costantino dated August 24, 2007 at page 3, ¶9, ¶10. In other words, Azria taught those skilled in the art that chlorobutanol was ineffective as a preservative at concentrations of 0.6% or less. As such, this disclosure taught away from using 0.6% or less of chlorobutanol in a calcitonin composition having chlorobutanol as the only preservative. Azria taught that such an amount rendered this preservative ineffective for its intended purpose.

Chlorobutanol is disclosed in both APC and Grebow as one of several preservatives for use in calcitonin formulations, e.g., thimerosol (0.001 – 0.01 w/v%), chlorobutanol (0.5 – 1.0 w/v%) and phenethyl alcohol (0.25 – 0.75 w/v%). *See* APC, page 3, lines 40-55 (describing seven different preservatives); Grebow, col. 12, lines 1-13 (describing nine different preservatives). When trying to capture all possible preservatives generally, both references refer to a broad range of 0.001 – 2.0% w/v regarding all possible preservative concentrations for every cited preservative. Regarding chlorobutanol in particular, however, APC and Grebow taught the use of this composition as a preservative, but at a concentration of 0.5 – 1.0 w/v%, *i.e.*, higher than the range of concentrations of chlorobutanol recited in Applicants' claims.

The Examiner relied on Example 9 in Grebow (col. 13), and presumably Example 3 in APC (page 4), to assert that these references taught the use of chlorobutanol at a concentration as low as 0.1 w/v%. These Examples, however, presented formulations having at least two different preservatives, *i.e.*, chlorobutanol at 0.1 w/v% and phenethyl alcohol at 0.2 w/v%. APC,

page 4, lines 45-47; Grebow, col. 13, lines 14-15. Thus, upon reading the references cited by the Examiner, one of skill in the art preparing a calcitonin formulation containing less than 0.5% w/v% chlorobutanol would have necessarily also included an additional preservative. An additional preservative would have been used because, as disclosed in Azria, at concentrations of 0.6% or lower, chlorobutanol was ineffective as a preservative. Because the Grebow Example cited by the Examiner included more than one preservative, the concentrations of each of the two preservatives in that Example were lower than otherwise presented ranges for these two preservatives elsewhere in APC and Grebow.

In other words, considered in their entireties, these references suggested that one needed less of any one preservative if the formulation also included a second preservative. Thus, those skilled in the art would not have read either APC or Grebow as teaching 0.1 w/v%—or any concentration of below 0.5% for that matter—of chlorobutanol in a calcitonin formulation, when the formulation contained chlorobutanol as the only preservative.

As noted above, Applicants' pending claims recite "consisting of." Thus, the recited compositions do not include a second preservative, *i.e.*, phenethyl alcohol, the second preservative present in Example 3 of APC and Example 9 of Grebow. Those Examples in APC and Grebow would not have taught or suggested making a calcitonin formulation having 0.1% w/v chlorobutanol and lacking phenethyl alcohol. Rather, one reading these Examples would have been motivated to include another preservative, such as phenethyl alcohol, if using chlorobutanol at a concentration less than the taught range of 0.5 – 1.0% w/v.

The Examiner takes the position that "[t]he fact that the APC reference and Grebow teach other preservative[s] is also not a consideration for the use of chlorobutanol as Grebow presents a specific example that has chlorobutanol as the ingredient for a preservative, regardless of the fact it had other ingredients in the composition." Office Action at 9. This position by the Examiner ignores the "consisting of" language in the pending claims. An issue here is whether the cited compositions in APC and Grebow contained an additional preservative. When read in their entireties, both references disclose the specific concentrations of chlorobutanol in particular, 0.5

– 1.0 w/v%, *i.e.*, higher than the range of concentrations of chlorobutanol recited in Applicants' claims, but when used in conjunction with another preservative, a lower concentration of chlorobutanol may be used. Thus, the specific example relied upon by the Examiner does not render obvious claims to calcitonin compositions with chlorobutanol as the only preservative at a concentration of between 0.25% and about 0.4% weight/weight.

It is well established that hindsight reasoning is impermissible to support an obviousness rejection:

> It is impermissible within the framework of section 103 to pick and choose from one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art.

In re Hedges, 228 USPQ 685, 687 (Fed. Cir. 1986). Indeed, the Examiner, in making his rejection, has used impermissible hindsight to selectively pick individual elements from the cited references to assert an alleged case of *prima facie* obviousness. To suggest now that one of ordinary skill in the art would arrive at the specific compositions claimed after reviewing the totality of the disclosures in Azria, APC and Grebow is a result of hindsight and not any teaching or suggestion in the references themselves.

For all these reasons, Applicants respectfully assert that the obviousness rejection is in error, and that claims 8, 12, 16 and 20-30 are patentable.

Respectfully submitted,

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By Jacq. D. Wright Bonilla

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 295-4792
Facsimile: (202) 672-5399

Jacqueline D. Wright Bonilla
Attorney for Applicant
Registration No. 45,239